HED DOC. NO. 013308

DATE: April 7, 1999

MEMORANDUM

SUBJECT: ***ACIFLUORFEN***- Report of the Hazard Identification Assessment Review Committee.

FROM: Paul Chin
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Pauline Wagner, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Virginia Dobozy, Risk Assessor
Reregistration Branch I
Health Effects Division (7509C)

PC Code: 114402

On January 19, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **acifluorfen** and selected the toxicological endpoints for acute and chronic dietary, occupational and residential (dermal and inhalation) exposure risk assessments. During this meeting, two issues, which required further evaluation of the available data, were unresolved. The issues were to support (or do not support) requiring a developmental neurotoxicity study based on a literature review of neurotoxicity data on structurally related compounds (oxyfluorfen, nitrofen, fomesafen, and lactofen) and to make susceptibility determination based on review of a second developmental toxicity study in rabbits (1976 study).

On February 11, 1999, the HIARC revisited acifluorfen to resolve the two remaining issues. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to **acifluorfen** as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's

conclusions are presented in this report.

Committee Members in Attendance

January 19, 1999

Members present were David Anderson, Bill Burnam, Virginia Dobozy, Pamela Hurley, Mike Ioannou, Tina Levine, Nicole Paquette, Kathleen Raffaele, PV Shah, Pauline Wagner, and Brenda Tarplee (Executive Secretary). Members in an absentia were Karen Hamernik, Susan Makris, Jess Rowland, and Nancy McCarroll. Data were presented by Paul Chin of Reregistration Branch I.. Also, in attendance were Whang Phang, Catherine Joseph, and Ed Budd.

February 11, 1999

Members present were David Anderson, Bill Burnam, Virginia Dobozy, Pamela Hurley, Mike Ioannou, Tina Levine, Sue Makris, Nicole Paquette, Kathleen Raffaele, Jess Rowland, Pauline Wagner, and Brenda Tarplee (Executive Secretary). Members in an absentia were Karen Hamernik, PV Shah, and Nancy McCarroll. Data were presented by Paul Chin of Reregistration Branch I. Also, in attendance were Whang Phang and S. Diwan.

Data Presentation: _____
and
Report Presentation Paul Chin
Toxicologist

Report Concurrence: _____
Brenda Tarplee
Executive Secretary

I. INTRODUCTION

ACIFLUORFEN (Sodium 5-[2-chloro-4-(trifluoromethyl) phenoxy]-2-nitrobenzoate) is the active ingredient of two herbicides, Tackle and Blazer, which were originally manufactured by two companies. Both Tackle and Blazer are currently registered for use on food crops.

Toxicological data are available on both products; however, the data on Tackle are more current, complete and acceptable. Therefore, discussions of the toxicology of acifluorfen are predominantly based on the data derived from the studies with Tackle, and where appropriate the data on Blazer are also utilized. It should be noted that Tackle contains about 20% to 24% of acifluorfen as the active ingredient, whereas Blazer contains approximately 40% of acifluorfen.

Acifluorfen induces an increase in combined malignant and benign tumor incidence in two mouse carcinogenicity studies employing different strains of mice (B6C3F1 and CR-CD-1) [HED Doc. No. 003410; 001099; 003963; 003409 (same as 003556)].

The HED Cancer Peer Review Committee (HED Doc. No. 007698 dated March 17, 1988) evaluated the toxicology data of this chemical and **classified it as a B2 carcinogen (probable human carcinogen). A value for Q_1^* was calculated to be 3.55×10^{-2}.**

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD) Subpopulation (Females 13+)

Study Selected: Developmental Toxicity Study in Rats **Guideline #:** 83-3(a)

MRID No.: 00122743

Executive Summary:

In a developmental toxicity study (MRID No. 00122743; Accession No. 071319), Tackle "2S" (22.4% a.i.) was administered to Crl:COBS CD (SD) BR rats (25/sex/dose) by intubation at doses of 0, 20, 90, or 180 mg/kg/day from gestation days 6 through 19. Three animals from the high-dose group died on test. Clinical signs, such as excessive salivation, urine-stained fur of the abdomen, rales, decreased motor activity and chromodacryorrhea were observed in the high-dose animals. Clinical signs, excessive salivation and piloerection, were also observed in the mid-dose animals. The mean body weights of the high-dose animals was significantly ($p<0.01$) decreased from gestation day 13 to sacrifice. The change in body weights of the high-dose animals over the treatment period (days 6-19) and over the entire gestational period (days 0-20) were 35% and 26%, respectively, lower than the control values.

The NOAEL for maternal toxicity is 20 mg/kg/day. The LOAEL for maternal toxicity is 90 mg/kg/day based on increase in clinical signs (including excessive salivation and piloerection).

A significant increase ($p < 0.0001$) in resorptions in the high-dose group and significant reduction ($p< 0.01$) in mean fetal weights for both the mid- and high-dose groups were observed. A significant increase ($p< 0.05$ or 0.01) in anatomical variations was seen in the mid- and high-dose groups. The variations included slightly dilated lateral ventricles of the brain, hemorrhage in the eyeball, slight dilation of the renal pelvis, hemorrhage in either the peritoneal cavity or subcutaneous spaces, and minor changes in ossification (such as incomplete ossification of supra-occipital sternebra or thoracic centra). **The NOAEL for developmental toxicity is 20 mg/kg/day; the LOAEL for developmental toxicity is 90 mg/kg/day based on the decreased fetal body weight and the increase in anatomical variations. This study is classified as ACCEPTABLE/GUIDELINE and satisfies the guideline data requirement for a developmental toxicity study (83-3a) in rats.**

Dose and Endpoint for Risk Assessment: NOAEL=20 mg/kg/day; LOAEL=90 mg/kg/day **based on the decreased fetal body weight and the increase in anatomical variations.**

Uncertainty Factor(s): An uncertainty factor of 100 was applied to account for inter-species extrapolation (10 x) and intra-species variability (10 x).

ACUTE RfD (females 13+) :

$$\frac{20 \text{ mg/kg/day}}{100 \text{ (UF)}} = 0.2 \text{ mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor(s): This endpoint is appropriate for females 13+ subpopulation only since the end point is an in utero affect.

This Risk Assessment is Required.

For General Population

Dose and Endpoint for Risk Assessment: No appropriate endpoint was identified for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure [dose].

Acute RfD: None.

B. Chronic dietary [Reference Dose (RfD)]

Study Selected: 2-generation reproduction study **Guideline #: 83-4**

MRID No.: 00155548

Executive Summary:

In a 2-generation reproduction study (MRID No.00155548), Tackle "2S" (21.1-21.6% a.i.) was administered to Crl:COBS CD (SD) BR Rats (35/sex/dose) in the diet at levels of 0, 25, 500, or 2500 ppm (0, 1.25, 25, or 125 mg/kg/day based on a conversion factor of 1 ppm = 0.05g/kg/day). During the premating period, body weights and/or body weight gains of P1 and F1 high-dose males and females were significantly decreased ($p<0.05$); the body weight decrease in high dose F1 females persisted throughout gestation and lactation (10-25% at various times of determination). In contrast, the food consumption in high dose animals was greater than that of the controls at majority of the measuring intervals. The food consumption in mid- and low-dose groups was comparable to that of the controls.

The test chemical did not significantly affect any of the reproductive parameters. **The NOAEL for reproductive toxicity is equal to or greater than 2500 ppm (125 mg/kg/day) the highest dose tested and the LOAEL is not established.**

Microscopically, in both generations P1 and F1 females, administration of Tackle at mid- and high-doses resulted in increased incidences of kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla. In high-dose second generation P1 males, there was a significant increase in the incidence of pelvic dilatation (hydronephrosis) when compared to the controls. **The NOAEL for parental toxicity is 25 ppm (1.25 mg/kg/day) and the LOAEL is 500 ppm (25 mg/kg/day) based on** kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla, in females of both generations.

In both generations of offspring, the body weight was significantly lower for high-dose litters (6-19% decrease for F1 and 11-26% decrease for F2) at birth and on lactation days 7, 14, and 21 when compared to the controls. Other offspring effects observed were as follows: Viability indices (percentage of liveborn pups that survived to day 4 postpartum) were lower in F1 generation only when compared to the controls. In F2 generation, the incidence of pups dying between lactation days 1 and 4 was significantly increased (3-3.4%) for the mid- and high-dose

groups when compared to the controls. In addition, in F2 generation, the incidence of grossly observed kidney lesions, primarily dilatation of the pelvis, was significantly increased at the high-dose level when compared to the controls. **The NOAEL for offspring toxicity is 25 ppm (1.25 mg/kg/day) and the LOAEL is 500 ppm (25 mg/kg/day) based on** decreased viability and increased incidence of kidney lesions, characterized predominantly by dilatation of pelvis in F2 generation. **This study is classified as Acceptable/Guideline and satisfies the guideline data requirement for a multi-generation reproduction study (83-4) in rats.**

Dose and Endpoint for Risk Assessment: NOAEL of 1.25 mg/kg/day based on kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla, in females of both generations.

Uncertainty Factor(s): An uncertainty factor of 100 was applied to account for inter-species extrapolation (10 x) and intra-species variability (10 x).

Chronic RfD = $\frac{\text{1.25 NOAEL (mg/kg/day)}}{\text{100 (UF)}}$ =0.013 mg/kg/day

Comments about Study/Endpoint/Uncertainty Factor(s):
The lowest NOAEL in the most sensitive species.

C. Occupational / Residential Exposure

1. Dermal Absorption

Percentage (%) Dermal Absorption: 20% dermal absorption (see comments below).

A dermal absorption factor of 20% was estimated by the HIARC. The reasons are the following:

A dermal penetration study in rats (**MRID No.:** 00156020) is available. The data indicated that the dermal absorption of acifluorfen following 10 hours exposure is 0.02% for doses of 10.2, 1.02 and 0.104 mg/rat. However, significant amounts of dose (1.3, 20 and 44% of doses at 10.2, 1.02 and 0.104 mg/rat, respectively) remained on the application site after washing which indicates some binding to the skin and, therefore, is still available for absorption. Because the duration of the study was only for 10 hours and up to 40% of the dose was still present at this measurement interval, it is presumed that there is a potential for continued absorption. Therefore, the HIARC recommended a dermal penetration value of 20%, which is an average value of the test material remaining on the skin at 10-hours post-treatment (after washing). This 20% value is also supported by a 32% absorption value extrapolated by comparing LOAELs of oral and dermal studies as shown below: In the 21-day dermal toxicity study (MRID No. 00122731), the LOAEL was 570 mg/kg/day based on mortality of 19/20

animals (both sexes) by day 8 of the study. In the developmental toxicity study in rabbits (MRID No. 107485), the LOAEL was 180 mg/kg/day based on mortality. A ratio of the LOAELs based on the same endpoint in the same species indicated an approximate dermal absorption rate of 32%.

$$\frac{\text{oral LOAEL 180 mg/kg/day}}{\text{dermal LOAEL 570 mg/kg/day}} \times 100$$

2. Short-Term Dermal (1 - 7 days)

Study Selected: Rat developmental toxicity study Guideline #: 83-3 (a)

MRID No.: 00122743

Executive Summary: See Acute Dietary.

Dose and Endpoint for Risk Assessment: Oral NOAEL of 20 mg/kg/day **based on the decreased fetal body weight and the increase in anatomical variations at** 90 mg/kg/day (LOAEL)**.**

Comments about Study/Endpoint: A 21-day dermal toxicity study in rats (MRID No. 00122731) is available. The HIARC, however, selected the oral developmental toxicity study because the concern for the developmental effects were seen in the rats and the fetal effects are not evaluated in the dermal toxicity study and thus the consequences of these effects of concern cannot be ascertained for the dermal route of exposure. Also, the developmental effects are presumed to occur after a single or multiple doses during the dosing period (12 days) which is appropriate for this exposure period of concern (1-7 days).

This Risk Assessment for Short-Term is Required.

3. Intermediate-Term Dermal (1-Week to Several Months)

Rat developmental toxicity study Guideline #: 83-3 (a)

MRID No. 00122743

Executive Summary: See Acute Dietary.

Dose and Endpoint for Risk Assessment: Oral NOAEL of 20 mg/kg/day **based on the decreased fetal body weight and the increase in anatomical variations at** 90 mg/kg/day (LOAEL)**.**

Comments about Study/Endpoint: See short term.

This Risk Assessment is Required.

4. Long-Term Dermal (Several Months to Lifetime)

The current use pattern does not indicate a concern for Long-Term exposure or risk.
This risk assessment is **NOT** required.

5. Occupational/ Residential Exposure—Inhalation (Any-Time Period)

Except for an acute inhalation toxicity study, the results of which place acifluorfen in Toxicity Category IV (LC_{50} > 6.9 mg/L), **no other studies are available via this route**. Therefore, the HIARC selected the oral NOELs of 20 mg/kg/day from developmental toxicity study in rats for Short-Term and Intermediate-Term inhalation risk assessments. Since an oral value is selected, route-to-route extrapolation should be as follows:

Step I. The inhalation exposure component (i.e., µg a.i/day) using a 100% absorption rate (default value) and an application rate should be converted to an **equivalent oral dose** (mg/kg/day)

Step II. The dermal exposure component (i.e., mg/kg/day) using a 20% dermal absorption value and an application rate should be converted to an **equivalent oral dose**. This dose should then be combined with the converted oral dose in Step I.

Step III. To calculate MOE's, the combined dose from Step II should then be compared to the oral NOEL of 20 mg/kg/day for both Short-Term and Intermediate-Term exposures.

This risk assessment is required for short and intermediate term inhalation exposure.

Based on the use pattern, Long-Term inhalation exposure risk assessment is not required.

D. Recommendation for Aggregate Exposure risk Assessments

For acute aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

For short- and intermediate-term aggregate exposure risk assessment, combine the average values from food + water together with short or intermediate dermal (corrected for %DA) + short or intermediate inhalation (corrected for %IA) exposure and compared to the oral NOAEL.

Based on the use pattern, chronic aggregate exposure risk assessment is not required.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

A MOE of 100 is adequate for occupational exposure and the MOEs for residential (dermal and inhalation) exposure will be determined during risk characterization by the FQPA Safety Factor Committee.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

Acifluorfen induces an increase in combined malignant and benign tumor incidence in two mouse carcinogenicity studies employing different strains of mice (B6C3F1 and CR-CD-1) [HED Doc. No. 003410; 001099; 003963; 003409 (same as 003556)]. The data were evaluated by the HED Cancer Peer Review Committee (HED Doc. No. 007698 dated March 17, 1988).

IV. MUTAGENICITY

Acifluorfen was negative for inducing mutations in four of six acceptable guideline studies of the standard battery of mutagenicity tests. These studies satisfy mutagenicity testing requirements. In addition to these studies, a microbial mutagenicity assay (MRID No. 41480101) and a CHO/HGPRT mutation assay (MRID No. 41480103) were submitted; however, these studies are currently being reviewed.

Acifluorfen was negative in the following studies:

In a bone marrow chromosomal analysis (MRID No. 00122741; Accession No. 071318), acifluorfen was negative in male Sprague-Dawley rats up to the highest dose tested (1.37 g/kg/day) administered for 5 consecutive days by oral gavage.

In a gene mutation assay in somatic cells in culture (MRID No. 00122739; Accession No. 071318), acifluorfen was tested for the ability to induce forward mutations at the thymidine kinase ($TK^{+/-}$) locus in mouse lymphoma cells with and without the metabolic activating system (S-9 fraction). Acifluorfen was negative up to a cytotoxic concentration of 387.3 ug/ml (without S-9) and127.6 ug/ml (with S-9). **This study is classified as unacceptable/guideline and does not satisfy the guideline data requirement for a mutagenicity study (84-2).** The study would be upgraded to acceptable if the positive control concentrations and the mutation frequencies are reported.

In a primary rat hepatocyte unscheduled DNA synthesis assay (MRID No. 00122742; Accession No. 071318), acifluorfen was negative up to a cytotoxic concentration of 50 ug/ml.

In a dominant lethal mutagenicity assay (MRID No. 00122738; Accession No. 071318), acifluorfen was negative in male Sprague-Dawley rats up to the highest dose tested (800 mg/kg/day) administered for 5 consecutive days by oral gavage and allowed to mate over a 7-week period.

Acifluorfen was positive in the following studies:

In a sex-linked recessive lethal test in Drosophilia melangaster MRID No. 00122737; Accession No. 071318), acifluorfen was positive in 2 parameters (Y chromosome loss and dominant lethal mutation assays) but negative in 3 parameters (somatic reversion of white-ivory, bithorax test of Lewis, and sex-linked lethal assays).

In a mitotic recombination assay with Saccahromyces cerevisiae (MRID No. 00148272; Accession No. 071318), acifluorfen was positive up to a cytotoxic concentration of 15 mg/plate without S-9 fraction.

V. FQPA CONSIDERATIONS

1. Neurotoxicity:

There are no neurotoxicity studies available for acifluorfen. Based on the published literature, there were no indications that structurally similar compounds **as a class** (oxyfluorfen, nitrofen, fomesafen, and lactofen) have neurotoxicity activity. However, neurotoxicity in the form of clinical signs (such as excessive salivation, urine-stained fur of the abdomen, rales, decreased motor activity and chromodacryorrhea) and slightly dilated lateral ventricles of the brain was observed in the developmental toxicity study in rats (see developmental toxicity study described below). Therefore, **in order to further define the neurotoxic potential in the developing fetus the HIARC recommended a developmental neurotoxicity study**.

2. Developmental Toxicity:

A. **Rat Developmental Toxicity Study**

Executive Summary:
In a developmental toxicity study (MRID No. 00122743; Accession No. 071319), Tackle "2S" (22.4% a.i.) was administered to Crl:COBS CD (SD) BR rats (25/sex/dose) by intubation at doses of 0, 20, 90, or 180 mg/kg/day from gestation days 6 through 19. Three animals from the high-dose group died on test. Clinical signs, such as excessive salivation, urine-stained fur of the abdomen, rales, decreased motor activity and chromodacryorrhea were observed in the high-dose animals. Clinical signs, excessive salivation and piloerection, were also observed in the mid-dose animals. The mean body weights of the high-dose animals was significantly ($p<0.01$) decreased from gestation day 13 to sacrifice. The change in body weights of the high-dose animals over the treatment period (days 6-19) and over the entire gestational period (days 0-20) were 35% and 26%, respectively, lower than the control values. **The NOAEL for maternal toxicity is 20 mg/kg/day. The LOAEL for maternal toxicity is 90 mg/kg/day based on increase in clinical signs (including excessive salivation and piloerection).**

A significant increase ($p < 0.0001$) in resorptions in the high-dose group and significant reduction ($p< 0.01$) in mean fetal weights for both the mid- and high-dose groups were observed. A significant increase ($p< 0.05$ or 0.01) in anatomical variations was seen in the mid- and high-dose groups. The variations included slightly dilated lateral ventricles of the brain, hemorrhage in the eyeball, slight dilation of the renal pelvis, hemorrhage in either the peritoneal cavity or subcutaneous spaces, and minor changes in ossification (such as incomplete

ossification of supra-occipital sternebra or thoracic centra). **The NOAEL for developmental toxicity is 20 mg/kg/day; the LOAEL for developmental toxicity is 90 mg/kg/day based on the decreased fetal body weight and the increase in anatomical variations. This study is classified as ACCEPTABLE/GUIDELINE and satisfies the guideline data requirement for a developmental toxicity study (83-3a) in rats.**

B. **Rabbit Developmental Toxicity Study**

Executive Summary: In a developmental toxicity study (MRID No. 00122744; Accession No. 071319), Tackle "2S" (22.4% a.i.) was administered to New Zealand White rabbits (16/sex/dose) by intubation at doses of 0, 3, 12, or 36 mg/kg/day from gestation days 6 through 29.

No statistically significant differences were noted in maternal body weights, body weight gains, numbers of corpora lutea, implantations/litter, resorptions, pregnancy rate, or implantation rate among all groups. Based on these data, the **NOAEL for maternal toxicity for acifluorfen is equal to or greater than 36 mg/kg/day (highest dose tested) and the LOAEL is not established**.

No evidence of treatment-related effects on mean fetal weights, anatomical variations, malformation, or alterations in sex ratios of surviving fetuses were seen.

Under the conditions of this study, **the NOAEL for developmental toxicity was equal to or greater than 36 mg/kg/day (highest dose tested). The LOAEL for developmental toxicity was not established.**

This study is classified as UNACCEPTABLE/GUIDELINE and does not satisfy the guideline data requirement for a developmental study (83-3b) in rabbits because the study showed no maternal or embryo/fetal toxicity.

C. Rabbit Developmental Toxicity Study (1976 study)

Executive Summary: A new executive summary and DER is being prepared for a developmental toxicity study (Accession No. 107485) with Blazer (39.85% a.i.). Based on the preliminary review of this study (memo from D. Anderson and S. Makris to P. Wagner and M. Ioannou, dated 1/28/99), acifluorfen caused treatment related embryo and fetal death but no specific CNS or other malformations. The NOAEL for maternal toxicity is 60 mg/kg/day and LOAEL is 180 mg/kg/day based on maternal death and maternal weight. The NOAEL for fetal toxicity is 60 mg/kg/day and LOAEL is 180 mg/kg/day based on resorptions and fetal death.

3. Reproductive Toxicity:

Executive Summary:
In a 2-generation reproduction study (MRID No.00155548), Tackle "2S" (21.1-21.6% a.i.) was administered to Crl:COBS CD (SD) BR Rats (35/sex/dose) in the diet at levels of 0, 25, 500, or 2500 ppm (0, 1.25, 25, or 125 mg/kg/day based on a conversion factor of 1 ppm = 0.05 mg/kg/day).During the premating period, body weights of P1 and F1 high-dose males and females were significantly decreased ($p<0.05$); the body weight decrease in high dose F1 females persisted throughout gestation and lactation (10-25% at various times of determination). In contrast, the food consumption in high dose animals was greater than that of the controls at majority of the measuring intervals. The food consumption in mid- and low-dose groups was comparable to that of the controls. The test chemical did not significantly affect any of the reproductive parameters. **The NOAEL for reproductive toxicity is equal to or greater than 2500 ppm (125 mg/kg/day) the highest dose tested and the LOAEL is not established.**

Microscopically, in both generations P1 and F1 females, administration of Tackle at mid- and high-doses resulted in increased incidences of kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla. In high-dose second generation P1 males, there was a significant increase in the incidence of pelvic dilatation (hydronephrosis) when compared to the controls. **The NOAEL for parental toxicity is 25 ppm (1.25 mg/kg/day) and the LOAEL is 500 ppm (25 mg/kg/day) based on** kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla, in females of both generations.

In both generations of offspring, the body weight was significantly lower for high-dose litters (6-19% decrease for F1 and 11-26% decrease for F2) at birth and on lactation days 7, 14, and 21 when compared to the controls. Other offspring effects observed were as follows: Viability indices (percentage of liveborn pups that survived to day 4 postpartum) were lower in F1 generation only when compared to the controls. In F2 generation, the incidence of pups dying between lactation days 1 and 4 was significantly increased (3-3.4%) for the mid- and high-dose groups when compared to the controls. In addition, in F2 generation, the incidence of grossly observed kidney lesions, primarily dilatation of the pelvis, was significantly increased at the high-dose level when compared to the controls. **The NOAEL for offspring toxicity is 25 ppm (1.25 mg/kg/day) and the LOAEL is 500 ppm (25 mg/kg/day) based on** decreased viability and increased incidence of kidney lesions, characterized predominantly by dilatation of pelvis in F2 generation. **This study is classified as Acceptable/Guideline and satisfies the guideline data requirement for a multi-generation reproduction study (83-4) in rats.**

4. Additional information from the literature

There are no additional neurotoxicity studies or developmental neurotoxicity studies via inhalation or any other routes from the published literature.

5. Determination of Susceptibility

The data base is complete for determining susceptibility. There are adequate developmental and reproduction studies.

The data provided indication of increased susceptibility of rats to *in utero* exposure to acifluorfen. In the prenatal developmental toxicity study in rats, developmental toxicity at 90 mg/kg/day was seen in the presence of minimal maternal toxicity at 90 mg/kg/day. **The NOAEL for developmental toxicity is 20 mg/kg/day; the LOAEL for developmental toxicity is 90 mg/kg/day based on the decreased fetal body weight and the increase in anatomical variations** including dilated lateral ventricles of the brain.

The data provided no indication of increased susceptibility of rabbits to *in utero* exposure to acifluorfen. In the prenatal developmental toxicity study in rabbits, no evidence of developmental toxicity was seen even in the presence of maternal toxicity at the highest dose tested.

In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

Neurotoxicity in the form of clinical signs (such as excessive salivation, urine-stained fur of the abdomen, rales, decreased motor activity and chromodacryorrhea) and slightly dilated lateral ventricles of the brain was observed in the developmental toxicity study in rats at the dose level of 90 and 180 mg/kg/day.

In conclusion, there is increased susceptibility for infants and children based on evidence of neurotoxicity from the developmental toxicity study in rats.

6. Recommendation for a Developmental Neurotoxicity Study

Based on the available data, the HIARC concluded that a developmental neurotoxicity study **is recommended.**

i. Evidence that suggest requiring a developmental neurotoxicity study:

The HIARC believes that here is evidence from the developmental toxicity study that there would be potential for developmental neurotoxicity. Evidence of treatment-related anomalies in the development of the fetal nervous system were observed in the prenatal developmental toxicity study in rats, at the maternally toxic oral dose of 90 mg/kg/day as indicated by a significant increase ($p < 0.0001$) in resorptions in the high-dose group and significant reduction ($p< 0.01$) in mean fetal weights for both the mid- and high-dose groups. A significant increase ($p< 0.05$ or 0.01) in anatomical variations was seen in the mid- and high-dose groups. The variations included slightly dilated lateral ventricles of the brain, hemorrhage in the eyeball, slight dilation of the renal pelvis, hemorrhage in either the peritoneal cavity or subcutaneous spaces, and minor changes in ossification (such as incomplete ossification of supra-occipital sternebra or thoracic centra). The HIARC can not discount the increased incidence of dilated lateral

ventricles of the brain because historical data for the incidence were not available.

In order to further define the neurotoxic potential in the developing fetus the HIARC recommended a developmental neurotoxicity study.

ii. Evidence that do not support a need for a developmental neurotoxicity study:

Neurotoxic compounds of similar structure were not identified.

7. Determination of the FQPA Safety Factor:

The HIARC, based on hazard assessment alone, recommends that the additional 10 x factor be retained because of the following:

Developmental toxicity study showed increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and the need for a developmental neurotoxicity study in rats.

The final recommendation on the FQPA Safety Factor, however will be made during the risk characterization by the FQPA Safety Committee.

VI. HAZARD CHARACTERIZATION

The toxicity data indicate that acifluorfen has low acute oral, dermal and inhalation toxicity. It is not a skin sensitizer. However, it causes severe eye and moderate skin irritation. The subchronic feeding study in rats and mice shows a decrease in body weight and signs of liver toxicity characterized by increased liver weight and increased incidence of cellular hypertrophy. The chronic feeding toxicity study in rats, mice and dogs demonstrated that acifluorfen induced liver toxicity (acidophilic cells in the liver and increased liver weight) and kidney toxicity (nephritis/pyelonephritis and increased kidney weight). The carcinogenicity data showed that acifluorfen produced an increase in incidence of liver and stomach tumors in mice but not in rats. Acifluorfen produced developmental toxicity in rats but not in rabbits and it did not affect reproductive parameters in rats. Acifluorfen showed mutagenic activity in 2 of the 6 assays.

Acifluorfen was rapidly absorbed orally and eliminated mainly in the urine (46-58% of the dose) and feces (21-41% of the dose). The major component present in urine and feces was unchanged acifluorfen and amine metabolite. No tissue accumulation was observed.

There is high confidence in the chronic RfD of 0.013 mg/kg/day. This was based on the NOAEL of 1.25 mg/kg/day from the 2-generation reproduction study in rat and uncertainty factor of 100. **The LOAEL for parental toxicity is 25 mg/kg/day based on** kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla, in females of both generations.

The database is adequate to evaluate FQPA assessment and consists of developmental studies in the rat and rabbit, and a two generation reproduction study in the rat. Based on the findings in the developmental toxicity study in rats, there appears to be an increased severity of effects noted in the offspring at maternally toxic doses. Neurotoxicity in the form of clinical signs (such as excessive salivation, urine-stained fur of the abdomen, rales, decreased motor activity and chromodacryorrhea) and slightly dilated lateral ventricles of the brain was observed in the developmental toxicity study in rats at the dose level of 90 and 180 mg/kg/day.

VII. DATA GAPS

Developmental neurotoxicity study in rat.

VIII. ACUTE TOXICITY

Acute Toxicity of Acifluorfen Technical[a]

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral (rats)[b]	00071887	LD_{50} =1540 mg/kg	III
	(dog)[b]	00071889	LD_{50} = 186 mg/kg	II
81-2	Acute Dermal (rabbits)	00122725	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	00122726	LC_{50} > 6.9 mg/L	IV
81-4	Primary Eye Irritation	00126597	Severe eye irritant	I
81-5	Primary Skin Irritation	00126597	Moderate dermal irritant	II
81-6	Dermal Sensitization	00122728	Not a skin sensitizer	

a: a 20.2-23.25% (W/V) aqueous dispersion of Acifluorfen technical (TACKLE)
b: a 40% (W/V) aqueous dispersion of Acifluorfen technical (BLAZER)

IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Female 13+)	**NOEL=20**	**Decreased fetal weight and** increased incidences of dilated lateral ventricles of the brain	**Developmental–rat** MRID No. 00122743
	UF=100	**Acute RfD = 0.2 mg/kg/day**	
Acute Dietary (General population)	**none**	**no endpoint established**	
	none	**none**	
Chronic Dietary	**NOEL=1.25**	**based on** kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla, in females of both generations	**2-generation reproduction–rat** MRID No.00155548
	UF=100	**Chronic =0.013 mg/kg/day**	
Short-Term [(a)] (Dermal)	**oral NOEL=20**	**Decreased fetal weight and** increased incidences of dilated lateral ventricles of the brain	**Developmental–rat** MRID No. 00122743
Intermediate-Term (Dermal)	**oral NOEL=20**	**Decreased fetal weight and** increased incidences of dilated lateral ventricles of the brain	**Developmental–rat** MRID No. 00122743
Long-Term (Dermal)	**None**	**Not required under the registered use patterns**	
Inhalation (short & intermediate) [(b)]	**oral NOEL=20**	**Decreased fetal weight and** increased incidences of dilated lateral ventricles of the brain	**Developmental–rat** MRID No. 00122743
Inhalation (long)	**None**	**Not required under the registered use patterns**	

a = Since an oral NOEL was selected, a dermal absorption factor of 20% should be used in route-to-route extrapolation.

b = Since an oral NOEL was selected, an inhalation absorption factor of 100% (default value) should be used in

route-to-route extrapolation.